REMARKS/ARGUMENTS

Claims 39-47, 49-52 and 55-58 are pending in this application. Claim 52 has been amended to remove reference to the recitation "wherein said polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction." All claims remain rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and written description. All rejections are respectfully traversed.

Rejections Under 35 U.S.C. §112, First Paragraph - Enablement

Claims 39-47, 49-52 and 55-58 remain rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the enablement requirement.

Briefly, the Examiner asserts that the Fong declaration was not persuasive and that "without further guidance correlating the observed stimulatory activity to a particular useful property, it would require undue experimentation to use PRO335". Applicants respectfully disagree.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. ([1, 2]. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[3] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[4, 5]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2)

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[1] MPEP §2164.0120.

[2] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

[3] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

[4] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important" [6,7] "Limitations and examples in the specification do not generally limit what is covered by the claims " MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[8]

The Disclosure provides sufficient information to enable the claimed invention

Claims 39-47, 49-52 and 55-58 are directed to a genus of nucleic acid sequences which are at least 80-99% identical to the: nucleic acid encoding the polypeptide of SEQ ID NO:290 or the nucleic acid of SEQ ID NO:289 and which have a specific and useful function (*i.e.* to the nucleic acids that encode for a genus of polypeptides that are "immunostimulants" useful for boosting the immune system of an animal).

Initially, Applicants submit that, both, the instant specification (in Example 74) and the Fong declaration (in previously submitted Exhibit A of the declaration) clearly refer to and incorporate by reference contents of the book "Current Protocols in Immunology, unit 3.12; edited by JE Coligan, AM Kruisbeek, DH Margulies, EM Shevach, W Stober, National Institutes of Health, Published by John Wiley & Sons, Inc. (1991) (referred to henceforth as "Current protocols"). "Current protocols" provides the detailed basic protocol, for instance, at least in Unit

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6 MPEP §2164.08.

7 *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971).

8 *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1372 (Fed. Cir. 1999) (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

3.12.6 entitled "T cell proliferation in mixed lymphocyte cultures" and further provides various other protocols for measuring T lymphocyte activation. It also provides methods for preparing cells and materials useful in the T lymphocyte activation assays and teaches that an MLR reaction can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, or, by observing blast formation, or by other methods well known in the art. Applicants submit that this information was readily available at the time of filing of the application, since the "Current protocols" reference was disclosed and incorporated by reference in its entirety at the time of filing.

Further, Applicants have provided native PRO sequence SEQ ID NO: 290. The specification further describes methods for the determination of percent identity between two amino acid sequences. In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO335 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences and methods of preparing the PRO polypeptides. Accordingly, one skilled in the art given the disclosure in the specification would be able to make the claimed amino acid sequence. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO: 290. Accordingly, one of ordinary skill could make the claimed invention without undue experimentation.

The Office action indicates that "no 'particular antigen' is identified in the specification; there is no guidance as to how PRO335 could be used to boost the response to any antigen". The Office action indicates regarding Current Protocols in Immunology (p. 3.12.11) that "the MLR only detects dividing cells instead of measuring true effector T-cell function.....it is not clear which T cell function is measured in proliferative assays....the proliferative response should be used solely as a general indicator of T cell reactivity".

Applicants respectfully submit that PRO335, just like any cytokine, contributes to stimulating the cellular responses (cellular immunity) rather than the humoral responses, of the immune system and therefore, is not directed to any "particular antigen". For instance, Unit 3.12.9 of Current Protocols in Immunology teaches how stimulator lymphocytes (which includes

dendritic cells) induce responder T cells and methods of preparing them. Further, Unit 3.12 discloses that "**(a) number of agents can specifically or nonspecifically induce T cell activation, resulting in cytokine production, cytokine receptor expression, and ultimately proliferation of the activated T cells**" (emphasis added).

The Examiner alleges that "further guidance is needed to correlate the observed stimulatory activity to a particular useful property."

Applicants submit that the MLR assay is a well accepted and useful assay for identifying immunostimulants. Based on the general knowledge in the art, for example, like Steinman, Thurner and Gubler, (previously submitted as exhibits with the Sherman Fong Declaration) one skilled in the art, at the effective date of the present application, would have known that any immunostimulant (just like cytokines) are very useful for stimulating or boosting the immune system of an animal, which in turn is useful, for example, to improve or increase immune surveillance in diseases like cancer. Cytokines like IL-2, etc. and other immunostimulants were well-known, researched and used to stimulate cellular immunity in various cancers (see references cited within Steinman, Thurner and Gubler *et al.*) at the effective filing date. In fact, Steinman *et al.* (Exhibit B) states "...**medicine needs therapies that enhance immunity or resistance to infections and tumors** (page 1, column 1, line 7; emphasis added)". In this regard, Applicants respectfully remind the Examiner that the skilled artisan in the field of Immunology and Immunotherapeutics, at the effective filing date of September 17, 1998, would likely be a person with a Ph. D. or M.D. degree, sometimes both, with extensive experience. Thus, one skilled in the art could easily test whether a native variant PRO335 protein was an immunostimulant in the MLR assay (as described in the Example 74 of the specification and in Current Protocols) and evaluate whether PRO335 was useful in the treatment of any cancer, as described in the art (see references cited within Steinman, Thurner and Gubler *et al.*). As the M.P.E.P. states, "[t]he fact that experimentation may e complex does not necessarily make it undue, if the art typically engages in such experimentation." [9] Thus, one would have known how to make and use the present invention at the effective date of the application.

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[9] M.P.E.P. 2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia* 774 F 2d 1104, 227 USPQ 428 (Fed. Cir. 1985)

Regarding the rejection based on the references Steinman and Thurner, the Examiner says that they "address the utility of dendritic cells but not of a stimulatory MLR." Applicants submit that, as indicated in Unit 3.12.9 of Current Protocols in Immunology, dendritic cells are stimulator lymphocytes that induce responder T cells and activate them to increase cytokine production, cytokine receptor expression, and ultimately proliferation of the activated T cells, all of which are measurable in different assays. In the current MLR assay, suspensions of responder T cells were cultured with irradiated- or mitomycin treated- allogenic stimulator lymphocytes and thymidine uptake was measured to give a measure of T cell proliferation (see Current protocols, Unit 3.12.9). Current Protocols also teaches how stimulator lymphocytes (which includes dendritic cells) induce responder T cells and methods of preparing them. Thus, based on this disclosure, one skilled in the art would know how to use dendritic cells in an MLR assay and how to measure T lymphocyte stimulation using thymidine uptake.

Regarding the rejection based on the Gubler reference, the Examiner says that it "describes the identification of IL-12 but uses MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant." Applicants respectfully disagree. In fact, the Gubler reference clearly teaches the MLR assay (see the footnote of Table 1, Fig. 3(upper panel) and related discussions in the results section), where PHA-activated lymphoblasts prepared from human PBMCs were used to measure lymphoblast proliferation in a tritiated thymidine assay . This assay was a key assay in identifying IL-12 as an immunostimulant for T lymphocytes with immunoenhancing effects. Again, this is evidenced since Gubler discloses in column 1, page 4143 that "we initiated a search for novel cytokines that would synergize with suboptimal concentrations of recombinant IL-2 **to activate cytotoxic lymphocytes *in vitro*** and thus might have **synergistic immunoenhancing effects** when administered together with recombinant IL-2 *in vivo*" (emphasis added).

Regarding the rejection based on the Peterson reference and the use of IL-12 as an immunostimulant, the Examiner says that Peterson's subsequent research "was clearly required to suggest that the molecule could be used in this fashion". Again, Applicants respectfully disagree. Even though the Peterson's reference was published after the effective filing date of the instant application, it is an enabling reference that supports the use of the immunostimulant IL-12 in the

treatment of a cancer, namely, melanoma. But the use of immunostimulants in the treatment of cancer was not concluded based on the Peterson studies. In fact, Gubler et al. independently indicate in column 1, page 4143, that "we initiated a search for novel cytokines that would synergize with suboptimal concentrations of recombinant IL-2 **to activate cytotoxic lymphocytes *in vitro*** and thus might have **synergistic immunoenhancing effects** when administered together with recombinant IL-2 *in vivo*" (emphasis added). Therefore, the Peterson reference is in fact a supportive and enabling reference for the use of immunostimulant molecules in the successful treatment of cancer.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Rejections Under 35 U.S.C. §112, First Paragraph - Written Description

Claims 39-43, 52, and 55-58 remain rejected for lack of written description for variants of the disclosed sequence. The Examiner asserts that "there is no particular function associated with leucine-rich repeats; proteins that have them are diverse in structure and function." Applicants respectfully traverse the rejection.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. [10, 11] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation

[10] MPEP §2164.01.

[11] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

is required, it is undue. [12] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue. [13, 14]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important" [15, 16]. "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[17]

Arguments

As noted above under the discussions on enablement, Applicants submit that utility for PRO335 and nucleic acids encoding it, as claimed, is based on its function as an

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[12] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

[13] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

[14] MPEP §2164.06.

[15] MPEP §2164.08.

[16] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

[17] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

immunostimulant (based on a positive hit in the MLR assay) and not on homology to proteins with leucine-rich repeats. Further, whether Applicants' were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification.

The teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan, as of the date the invention was made. The instant invention, defined by the claims, concerns nucleic acids having 80%, 85%, 90%, 95% or 99% sequence identity with the disclosed nucleic acid of the polypeptide of SEQ ID NO: 290 or the SEQ ID NO: 289 nucleic acid, which have been reduced to practice and "wherein the polypeptide encoded by said nucleic acid is an immunostimulant." Thus, based on the discussions above, the description of the MLR assay, the Sherman Fong Declaration and the attached articles therein, the skilled artisan would have reasonably concluded that Applicants had possession of the claimed polypeptides at the effective filing date.

Hence, Applicants submit that this rejection should be withdrawn.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C79**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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